Integrated Stress Response Activity Marks Stem Cells in Normal Hematopoiesis and Leukemia.

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Public Summary:
Blood or hematopoietic stem cells within the bone marrow are responsible for life-long maintenance of the adult blood system, providing the basis for clinical bone marrow or stem cell transplantation. However, mechanisms regulating their life-long maintenance and function are still poorly understood. In this paper, we identify a role for the integrated stress response pathway activity in HSC function. Leukemic stem cells also display similar pathway activity, suggesting new approaches to identify and targeted these relapse-causing stem cell populations.

Scientific Abstract:
Lifelong maintenance of the blood system requires equilibrium between clearance of damaged hematopoietic stem cells (HSCs) and long-term survival of the HSC pool. Severe perturbations of cellular homeostasis result in rapid HSC loss to maintain clonal purity. However, normal homeostatic processes can also generate lower-level stress; how HSCs survive these conditions remains unknown. Here we show that the integrated stress response (ISR) is uniquely active in HSCs and facilitates their persistence. Activating transcription factor 4 (ATF4) mediates the ISR and is highly expressed in HSCs due to scarcity of the eIF2 translation initiation complex. Amino acid deprivation results in eIF2alpha phosphorylation-dependent upregulation of ATF4, promoting HSC survival. Primitive acute myeloid leukemia (AML) cells also display eIF2 scarcity and ISR activity marks leukemia stem cells (LSCs) in primary AML samples. These findings identify a link between the ISR and stem cell survival in the normal and leukemic contexts.

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